Communication

A Versatile Approach for the Asymmetric Synthesis of 3-Alkyl-isoindolin-1-ones†

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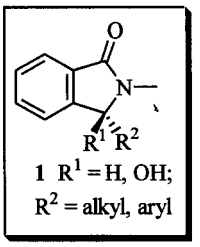
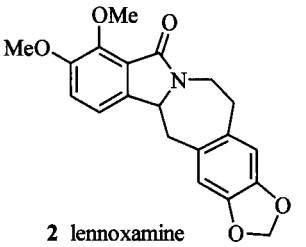
A flexible approach to (*R*)-3-alkyl-isoindolin-1-ones and (*R*)-3-aryl-isoindolin-1-ones via a diastereoselective reductive-alkylation is described. Present method is versatile in scope, allowing the easy introduction of various C-3 substituents by Grignard addition to phthalimide derived from (*R*)-phenylglycinol. 3-Alkyl-3-hydroxy-isoindolin-1-ones can also be obtained in the first step of the present method.

Keywords isoindolin-1-one, asymmetric synthesis, phenylglycinol, reductive alkylation, phthalimide

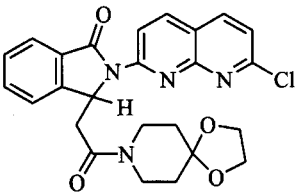
3-Substituted isoindolin-1-ones (2,3-dihydro-1*H*-isoindolin-1-ones) of general structure (**1**) constitute the key structural feature of a large number of bioactive molecules of natural or synthetic origin. For example, lennoxamine (**2**),[1] nuevamine and chilenine are alkaloids isolated from various barberries species, pazinaclone (**3**) is an anxiolytic drug candidate,[2] and chlortalidone (**4**) is a diuretic and antihypertensive drug.[3] Besides, (*R*)- and (*S*)-3-methyl-1*H*-isoindolin-1-ones have been shown to be valuable chiral auxiliaries.[4] As a result, the chemistry of 3-alkyl-isoindolin-1-ones has attracted much current attention, and a number of valuable synthetic methods have been developed.[5]



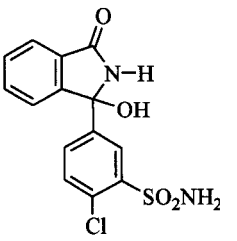
1 R^1 = H, OH; R^2 = alkyl, aryl



2 lennoxamine



3 pazinaclone



4 chlortalidone

However, in sharp contrast to the great progress made in the field of asymmetric synthesis in the last decade, the methods for the asymmetric synthesis of simple 3-alkyl-isoindolin-1-ones and 3-aryl-isoindolin-1-ones in high *ee* remained largely unexplored. The first paper on the asymmetric synthesis of (*R*)-3-methyl-isoindolin-1-one (**6a**) was reported by Oppolzer in 1990 (Scheme 1),[4a] and the second by Fujisawa is in 1993.[4d] It took several years before the appearance of the other methods by Allin (Scheme 2)[6] and by us[7,8] in 1999. Until 2000, only two 3-alkyl-1*H*-isoindolin-1-ones (namely 3-methyl-1*H*-isoindolin-1-one and 3-phenyl-1*H*-isoindolin-1-one) with high *ee* have been obtained by asymmetric synthesis. Oppolzer's method (Scheme 1)[4a-c] called for the use of *N*-acyl 1-phenylethylamine as the starting material, is thus limited to the synthesis of 3-methyl-1*H*-isoindolin-1-one (**6a**);[4a] Fujisawa's method[4d] is limited to the synthesis of 1-substituted 3-allyl-isoindolin-1-one; Allin's method (Scheme 2)[6] seems to be more flexible, however,

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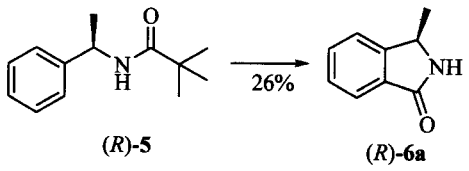
Scheme 1 Oppolzer's method

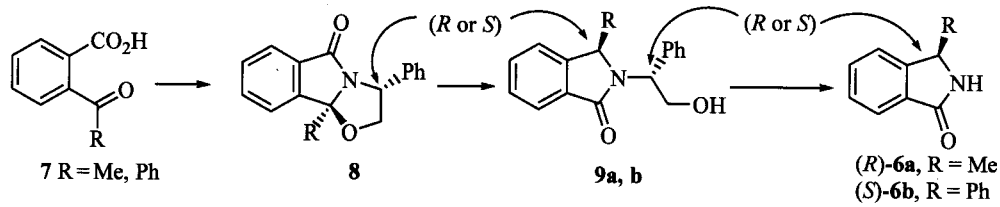


due to the not easy availability of the starting material, in addition to the known 3-methyl-1*H*-isoindolin-1-one (**6a**) (obtained from **9a** in the followed three-step procedure: MsCl, NEt_3; NaOEt, EtOH; HCl (3 mol/L), EtOH-H_2O, 80 ℃), only 3-phenyl-1*H*-isoindolin-1-one (**6b**) (obtained by heating **9b** in conc. H_2SO_4) has thus been prepared by this method.[6] More recently, Enders reported another approach to 3-aryl substituted 2,3-dihydro-1*H*-isoindolin-1-ones via a tandem nucleophilic 1,2-addition ring closure procedure from SAMP / RAMP hydrazones .[9]

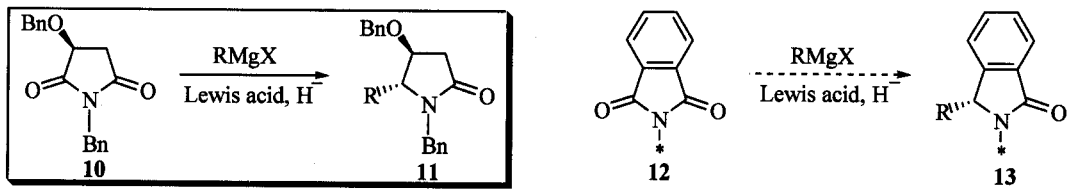
Consequently, versatile and flexible method for the asymmetric synthesis of 3-alkyl-isoindolin-1-ones is highly desirable.

Previously, we developed a highly regio- and diastereo-selective reductive alkylation of optically active imides (Scheme 3, **10**→**11**)[10] for the asymmetric synthesis of 2-pyrrolidinones, pyrrolidines and β-hydroxy γ-amino acids. As an extension of this methodology, we began, in 1998, to explore the similar reductive alkylation for a versatile and flexible approach to optically active 3-alkyl-isoindolin-1-ones (**12**→**13**).[7,8] Central to our approach has been the asymmetric induction, for this purpose, (*R*)-phenylglycinol was selected as the chiral auxiliary, which was expected to display an *exo*-cyclic 1,3-asymmetric induction. We wish to report herein our findings in the context.

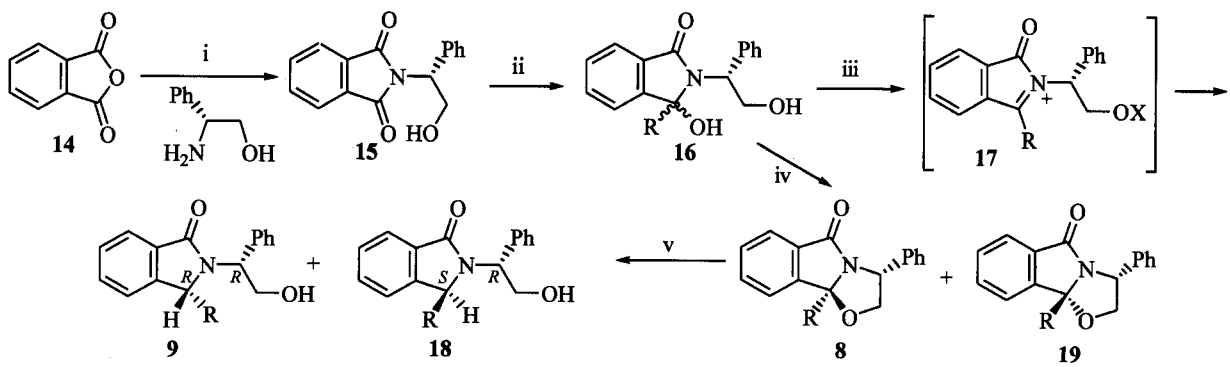
Scheme 2 Allin's method



Scheme 3



Scheme 4



Reagents and conditions: (i) neat, 150 ℃, 96%; (ii) RMgX (**a**, R = Me; **b**, R = Ph; **c**, R = Et; **d**, R = *n*-Bu; **e**, R = *i*-Bu; **f**, R = n-C_7H_{15}; **g**, R = Bn), THF, -15 ℃, 87%—96%; (iii) Et_3SiH, $F_3B{\cdot}OEt_2$, CH_2Cl_2, -78 ℃, 61%—98%; (iv) *p*-TsOH (cat.), 86%—94%; (v) Et_3SiH, $TiCl_4$, CH_2Cl_2, -78 ℃, 83%—99%.

Our method is displayed in Scheme 4. The requisite chiral (*R*)-phthalimide derivative **15** was obtained in high yield by heating a mixture of phthalic anhydride and (*R*)-phenylglycinol under solvent free conditions.[11] Treatment of phthalimide derivative **15** with an excess of methyl magnesium iodide smoothly led to the desired α-hydroxylactam **16a** (Table 1, Entry 1) as a diastereomeric mixture in a ratio of 35:65. The stereochemistry of the isomeric **16a** was not assigned. Although the two diastereomers can be separated by column chromatography on silica gel, the mixture was used in the next step as it was. Since the followed reductive dehydroxylation was expected to proceed via the intermediate of the *N*-acyliminium ion **17a**,[12] both the diastereomeric aza-carbinols **16a** would gave the same *N*-acyliminium ion **17a**. Indeed, when the diastereomeric mixture of **16a** was subjected to boron trifluoride etherate mediated triethylsilane reduction,[10,13] the diastereoisomer **9a** formed predominately. The diastereomeric ratio of **9a**/**18a** was 87:13 according to the chromatographic separation. Extension of this procedure to other Grignard reagents led to the corresponding products **9b**—**9g** and **18b**—**18g** in diastereoselectivity varied from 91:9—71:29 (Table 1, Entries 2—7). The stereochemistry of the major diastereoisomer **9** obtained from the present reductive-alkylation procedure was ascertained by a single-crystal X-ray crystallographic analysis of compound (3*R*,1*R*)-**9d**[14] (Fig. 1). The stereochemistries of the major diastereomers **9a**—**9c** and **9e**—**9g** deduced by comparison their ^{1}H NMR spectra with that of **9d** were shown in the general structure **9**.

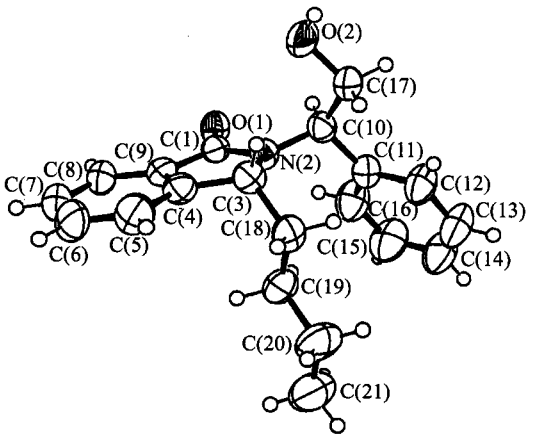


Fig. 1 Crystal structure of (3*R*,1*R*)-**9d**.

Although in all cases the reductive alkylation exhibited reasonable to good exo-cyclic 1,3-asymmetic induction, in light of the excellent asymmetric induction observed in the diastereoselective reductive ring-opening of bicyclic and tricyclic lactams, as demonstrated by Meyers[13d,e] and more recently, by Allin *et al.*,[6] a better diastereo-selection could be expected. The most obvious way to achieve higher diastereoselectivity would reside on the transformation of aza-carbinols **16** to tricyclic lactams **8** or **19**. Although the literature precedents showed that such conversion is, in some cases,[11,15] difficult to accomplish, we were delight to find that in our case, such transformation could be achieved readily just by stirring,

Table 1 Preparation of 3-substituted isoindolin-1-ones (**9**) via the reductive alkylation of (*R*)-malimide (**15**)

Entry	Starting material	RMgX	Product (yield, %)	Isoindolin-1-one (yield, %)	**9**:**18** ratio[a]
1	**15**	MeMgI	**16a** (87)	**9a** + **18a** (92)	87:13
2	**15**	PhMgBr	**16b** (90)	**9b** + **18b** (90)	71:29
3	**15**	EtMgBr	**16c** (96)	**9c** + **18c** (95)	85:15
4	**15**	*n*-BuMgBr	**16d** (87)	**9d** + **18d** (98)	84:16
5	**15**	*i*-BuMgBr	**16e** (91)	**9e** + **18e** (85)	91:9
6	**15**	*n*-C_7H_{15}MgBr	**16f** (88)	**9f** + **18f** (61)	77:23
7	**15**	BnMgCl	**16g** (96)	**9g** + **18g** (97)	81:19

[a] The diastereomeric ratio was determined by chromatographic separation.

Table 2 Preparation of 3-substituted isoindolin-1-ones (**9**) via the reductive deoxygenation of tricyclic lactams **8**

Entry	Starting material	Cyclic product (yield, %)	**8**:**19** ratio[a]	Isoindolin-1-one (yield, %)	**9**:**18** ratio[a]
1	**16a** (R = Me)	**8a** (92)	96:4	**9a** + **18a** (83)	95:5
2	**16e** (R = *i*-Bu)	**8e** (50)	*ca.* 100:0	**9e** + **18e** (65)	*ca.* 100:0

[a] The diastereomeric ratio was determined by chromatographic separation.

at room temperature, aza-carbinol **16a** under acidic conditions (Scheme 4). Thus, tricyclic lactam **8a** was formed in exellent diastereoselectivity (Table 2, Entry 1). The fact that heating the diastereomeric mixture of aza-carbinol **16a** under acidic conditions affords the same diastereoisomer as that obtained at room temperature might implicate that the isolated tricyclic lactam **8a** is the thermodynamically more stable diastereoisomer, which is also the same as that obtained by an alternative method.[6] The observed stereochemistry preference during the formation of **8a** is well documented in the literature for bicyclic 1,3-oxazololactams[16a,b] and 1,3-oxazolopyrrolidines.[16c] The reductive ring-opening of **8a** under standard conditions ($TiCl_4$, Et_3SiH, CH_2Cl_2, -78 ℃)[13d,e] afforded, as anticipated, **9a** and **18a** in excellent diastereoselectivity (**9a**:**18a** = 95:5). Similarly, the reductive ring opening of **8e** gave **9e** as the sole diastereomer. However, **8e** was formed in only 50% yield from **16e** due to dehydrative side reaction. Thus, in the present method, the two variations depicted in Scheme 4 are complementary in view of chemical yield and stereoselectivity. The chiral auxiliary on nitrogen of 3-alkyl-isoindolin-1-ones (**9**) could be cleaved under racemization-free conditions to afford 3-alkyl-isoindolin-1-ones[6,17] as demonstrated for **9a** and **9b** (Scheme 2).[6,17]

In summary, a versatile and flexible approach to (*R*)-3-alkyl-isoindolin-1-ones and (*R*)-3-aryl-isoindolin-1-ones of general structure (**1**) is developed via a highly diastereoselective reductive-alkylation procedure. This method is versatile in scope, since various C-3 substituents can be introduced easily by Grignard reaction. 3-Substituted 3-hydroxy-isoindolin-1-ones (**16**) can also be obtained from the Grignard addition. The application of present method to the asymmetric synthesis of 3-alkyl-isoindolin-1-one based bioactive and/or natural products is in progress.

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(b) (3*R*,1*R*)-**9a**: $[\alpha]_D^{20}$ 88.6 (*c* 2.26, CH_2Cl_2) {Lit. $[\alpha]_D$ 21.3 (*c* 2.34, CH_2Cl_2);[6c] $[\alpha]_D$ 84 (*c* 0.9, CH_2Cl_2)[14a]}. (3*R*,1*R*)-**9b**: $[\alpha]_D^{20}$ −75.2 (*c* 3.2, CH_2Cl_2) {Lit.[6c] for (3*S*,1*S*)-**9b**: $[\alpha]_D$ 84.8 (*c* 3.3, CH_2Cl_2)}. (3*R*,1*R*)-**9g**: $[\alpha]_D^{20}$ 53.6 (*c* 1.1, $CHCl_3$) {Lit.[14a] $[\alpha]_D$ 66 (*c* 0.5, CH_2Cl_2)}.
(c) Selected data for **9d**: m.p. 130—132 ℃; $[\alpha]_D^{20}$ 61.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.64—0.74 (m, 1H, $CH_2CH_2CH_2$), 0.80 (t, *J* = 7.3 Hz, 3H, CH_3), 1.06—1.16 (m, 1H, $CH_2CH_2CH_2$), 1.16—1.28 (m, 2H, $CH_2CH_2CH_3$), 1.86—2.01 (m, 2H, CH_2CH_2-CH_2), 4.11 (dd, *J* = 3.2, 12.4 Hz, 1H, CH_2OH), 4.39 (dd, *J* = 2.9, 5.2 Hz, 1H, $CCHCH_2$), 4.48 (dd, *J* = 8.0, 12.4 Hz, 1H, CH_2OH), 4.66 (dd, *J* = 3.2, 8.0 Hz, 1H, PhCHN), 7.24—7.40 (m, 6H, ArH), 7.50 (t, *J* = 7.45 Hz, 1H, ArH), 7.56 (t, *J* = 7.45, 1.1 Hz, 1H, ArH), 7.88 (d, *J* = 7.45 Hz, 1H, ArH); IR (KBr) ν: 3361, 1716, 1652, 1614, 1470, 1408 cm^{-1}; MS (LCQ) *m*/*z* (%): 310 (MH^+, 100). Anal. calcd for $C_{20}H_{23}NO_2$: C 77.69, H 7.49, N 4.45; found C 77.34, H 7.47, N 4.53.

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